Heterogeneity of Risk for Melanoma and Pancreatic and Digestive Malignancies

A Melanoma Case–Control Study

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BACKGROUND. Data addressing the interfamilial heterogeneity of melanoma are limited. In the current study, the authors assessed melanoma risk according to family history of melanoma and other melanoma-associated malignancies and evaluated the familial heterogeneity of melanomas, pancreatic malignancies, and gastrointestinal malignancies.

METHODS. The authors obtained patient histories of malignancy in first-degree relatives as part of a clinic-based case–control study. The case group included 737 newly diagnosed patients with invasive melanoma, and the control group included 1021 outpatients from clinics at the same medical centers. To assess heterogeneity of risk among families affected by melanoma, a nonparametric method was used to detect extrabinomial variation. In addition, selected patients with melanoma (n = 133) were tested for germline mutations in *CDKN2A*.

RESULTS. The adjusted odds ratio associated with a family history of melanoma was 1.7 (95% confidence interval, 1.1–2.7). Family histories of pancreatic, gastrointestinal, brain, breast, or lymphoproliferative disease did not increase the risk of melanoma significantly. Among case families, significant evidence of familial heterogeneity was found for melanomas, but not for pancreatic or gastrointestinal malignancies. Two mutations in *CDKN2A* previously associated with melanoma risk were identified among the 133 patients tested in the case group; mutation detection did not differ between families with low and high heterogeneity scores.

CONCLUSIONS. Familial heterogeneity testing in the study population did not improve the selection of high-risk families for genetic study. Even in a large case–control study, few families that had multiple members with melanoma were identified, and family members with pancreatic malignancies were rare. ***Cancer* 2004;101:2809–16.** *Published 2004 by the American Cancer Society.**

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Melanoma is a complex and heterogeneous disease that has host-related, genetic, and environmental factors contributing to its etiology.[1,2] This complexity may explain in part the wide variation across populations in terms of the percentage of patients with mela-

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noma who report a family history of melanoma.[3] Interfamilial variation in the risk of melanoma (i.e., familial heterogeneity) suggests that genetic or environmental factors related to family membership contribute to the observed variability in disease risk.[4,5] By assessing heterogeneity, investigators can evaluate the intrafamilial aggregation of disease to identify families whose members have a greater-than-expected risk of disease. Data are limited for determining whether familial heterogeneity for melanoma occurs in different populations and is useful for identifying families that have a greater risk for mutations in melanoma susceptibility genes. Within the highly sun-exposed Australian population, familial heterogeneity tests have been shown to successfully select families for genetic study.[5,6] Relatives in high-risk families (as identified by heterogeneity testing) also were significantly more likely to have reported decreased tanning ability, light skin color, and more nevi compared with relatives in non-high-risk families.[5]

Two genes, *CDKN2A* and *CDK4*, have been implicated in the etiology of melanoma. Germline *CDKN2A* mutations that cosegregated with disease have been found in ~20% of all melanoma-prone families evaluated,[7] and 3 families worldwide have been reported to have cosegregating *CDK4* mutations.[8,9] The likelihood of finding a *CDKN2A* mutation in the family increases as the number of family members with melanoma increases.[2] Among families with known germline *CDKN2A* mutations, the risk of melanoma varies widely according to geographic location.[10] These mutations however, have been shown to be responsible for only a small percentage of melanomas occurring outside of melanoma-prone families. Within the largest population-based study conducted to date,[5,6] the frequency of germline *CDKN2A* mutation carriers was 10.3% in the families that exhibited the highest heterogeneity scores but was relatively low overall (0.2%).[6]

In the current large, clinic-based case–control study, we examined evidence for heterogeneity of risk for melanoma and other malignancies (pancreatic, digestive, breast, brain, and lymphoproliferative malignancies, as well as soft tissue sarcoma) that are believed to cluster in melanoma-prone families.[11–19] We also assessed germline *CDKN2A* mutation status in a subset of patients in the case group.

MATERIALS AND METHODS

Study Population

The current case–control study was approved by the institutional review boards of the National Cancer Institute (Bethesda, MD), Westat Inc. (Rockville, MD), the University of California–San Francisco (San Francisco, CA), and the University of Pennsylvania (Philadelphia, PA). Each participant provided informed consent.

Eligible patients (ages 20–79 years), who were ascertained without regard to family history, were newly diagnosed with invasive cutaneous melanoma between January 1, 1991, and December 31, 1992, at the Pigmented Lesion Clinic of the Hospital of the University of Pennsylvania or the Melanoma Clinic of University of California–San Francisco. The response rate among these patients (who constituted the case group) was 96%.[20] All diagnoses of the index melanoma were confirmed by histologic review. The control group was recruited from 12 clinics (including ambulatory care, internal medicine, endocrinology, cardiology, and otolaryngology clinics) with catchment areas similar to those of the participating melanoma clinics. A stratified random-sampling scheme was used to select control participants who had the same age, race, gender, and geographic distributions as case participants did. The response rate among the control group was 84%.[20] Data collection procedures have been described in detail elsewhere.[20] In brief, all participants underwent a 45-minute in-person interview to obtain information regarding melanoma risk factors, a full-body skin examination for the assessment of nevus type and number, and nevus photography. Part of the interview dealt with family structure and cancer status (with age at diagnosis) of first-degree relatives (parents, siblings, and offspring). Probands (2 cases and 3 controls) who could not provide information on age or cancer diagnoses for any relatives were excluded from these analyses, leaving 737 melanoma case families, who had a total of 4640 first-degree relatives, and 1021 control families, who had a total of 6107 first-degree relatives. Among participating probands, 22 cases and 10 controls had a previous diagnosis of melanoma. To reduce the ascertainment bias, only information about relatives was used in the heterogeneity analyses. For relatives, reported diagnoses of malignancy were not validated, and data on risk factors relating to skin phenotypes or exposure were not collected.

Statistical Methods

Assessment of heterogeneity in case families

Heterogeneity in risk among melanoma families was assessed using a nonparametric method to detect extrabinomial variation.[21,22] Quantification of a family's melanoma risk was based on the observed deviation from the expected incidence of melanoma, taking into account family size and risk covariates (age, gender, and birth cohort) for family members.[5,6,22] A standardized familial risk statistic was calculated using the observed and expected disease distributions.

An extension of this approach was used to calculate the aggregate familial risk of pancreatic or gastrointestinal malignancies, either alone or in combination with melanoma. The malignancies (and combinations of malignancies) investigated were as follows: melanoma, pancreatic cancer, digestive cancers (pancreatic, esophageal, gastric, small and large intestinal, rectal, rectosigmoid junction, anal, hepatic, gallbladder, and other biliary cancers), melanoma plus pancreatic cancer (melanoma-pancreatic), and melanoma plus digestive cancer (melanoma-digestive). In a comparison performed to evaluate whether cases were systematically reporting more cancers in relatives than would be expected, all reported cancers (except basal cell carcinoma and squamous cell carcinoma of the skin) were evaluated simultaneously using the same methodology.

To evaluate melanoma risk, we used the following approach. In the *i*th family with *j* members and cancer or cancer combination *k*, the test statistic (T_{ik}) takes the following form:

$$T_{ik} = \frac{\sum_j O_{ijk} - \sum_j \left(\sum_k CI_{ijk} \right)}{\sqrt{\sum_j \left[\left(\sum_k CI_{ijk} \right) * \left(1 - \left(\sum_k CI_{ijk} \right) \right) \right]}},$$

where O_{ijk} is the disease status (0 or 1) of each family member for melanoma, pancreatic malignancy, digestive malignancy, melanoma–pancreatic malignancy, or melanoma–digestive malignancy, and CI_{ijk} is the cumulative lifetime incidence of the *j*th member of the *i*th family to develop cancer *k*. The null hypothesis was that an individual's probability of developing melanoma was not dependent on family history (i.e., disease risk was homogeneous), such that T_{ik} would have a mean of 0 and a variance of 1.[22]

Relatives of the study participants were located throughout the United States. To adjust for birth cohort effects, we used Connecticut incidence rates (dating back to 1935) to measure cumulative incidence rates for individual malignancies and malignancy combinations.[23,24] Rates were calculated by dividing case counts by appropriate population estimates and were specified as events per 1000 person-years. Rates were listed for 5-year calendar periods between 1925 and 1994. The 1935–1939 rates were used for the calendar periods 1925–1929 and 1930–1934. The rates for 1985–1989 and 1990–1992 were calculated on the basis of cases and populations for the period 1984–1986. Ages were matched to within 5 years for all individuals, and birth cohorts were matched to within 5 years for all individuals who were born after 1925. The combined expected disease distribution was calculated as the sum of the individual expected values for melanoma and the other cancer(s) under investigation.

In brief, the methodology used to evaluate familial heterogeneity in risk among relatives used a probability distribution created by generating 1000 random permutations of the members of the 737 case families.[5,22] In each permutation, all case families were reconstructed into hypothetic families of the same size as the case family by randomly replacing each relative with an individual matched with respect to age, gender, and birth cohort from the case population. T_{ik} and the variance in T_{ik} were calculated for each of the 737 case families in the original sample and for every reconstructed family in each of the 1000 permutations. In an analysis of excess risk, an observed variance falling above the 950th position of the permuted variances indicated that T_{ik} had significantly greater variation in the case population than would be expected under the null hypothesis (1-sided $\alpha = 0.05$).

Comparison of cases and controls

Reported occurrences of malignancy in case relatives versus control relatives were compared by using family histories of different malignancies as the variables of interest. For family histories of malignancies other than melanoma, analyses were stratified according to family history of melanoma. We estimated relative risks by calculating odds ratios with 95% confidence intervals (95% CIs) using EPITOME software.[25] To assess the risk associated with family history of melanoma, BMDP logistic regression models controlled simultaneously for age, gender, study site, and dysplastic nevi.[26] Dysplastic nevi were a major risk factor for melanoma in the current data set[20] and have frequently been reported to be associated with melanoma risk within families.[2]

Mutation Detection

This study was conducted before the identification of high-risk melanoma susceptibility genes. During the approval process, funding for biologic specimen collection was limited due to the associated costs. A subpopulation of patients with melanoma ($n = 133$) were asked to provide blood samples for molecular studies, with this subset being weighted according to either family history of melanoma or multiple primary melanoma. Most samples were sequenced for germline *CDKN2A* mutations at the National Cancer Institute. Other samples that had been tested previously were sequenced either at the University of Toronto (Toronto, Ontario, Canada) or under a contract with GeneLogic (Gaithersburg, MD). Sequencing was performed under slightly different conditions at each of the three laboratories, and information regarding spe-

TABLE 1
Distribution of Probands by Gender and Age and Distribution of Family Members by Relationship

	No. of individuals (%)	
Group	Cases	Controls
Probands		
Gender		
Male	406 (55.1)	557 (54.6)
Female	331 (44.9)	464 (45.4)
Age (yrs)		
20–29	55 (7.5)	94 (9.2)
30–39	136 (18.4)	202 (19.8)
40–49	204 (27.7)	233 (22.8)
50–59	125 (17.0)	205 (20.1)
60–69	139 (18.9)	167 (16.4)
≥70	78 (10.6)	120 (11.7)
Relatives		
Total	4640 (100.0)	6107 (100.0)
Mothers	733 (15.8)	1018 (16.7)
Fathers	733 (15.8)	1018 (16.7)
Sisters	846 (18.2)	1180 (19.3)
Brothers	901 (19.4)	1207 (19.8)
Daughters	724 (15.6)	858 (14.0)
Sons	703 (15.2)	826 (13.5)

cific primers and conditions can be requested and obtained from the authors. Quality-control samples with known positive mutation status were used to compare results across laboratories.

RESULTS

The case and control participants were similar in terms of gender, age, and number of family members reported (Table 1). In addition to having similar numbers of relatives, the family sizes of the cases and controls were equivalent (data not shown). The distributions of case and control families with the various malignancies of interest are summarized in Table 2. Eight percent of melanoma case participants, compared with 4% of control participants, reported having first-degree relatives with melanoma (Table 2); 3 case participants and 1 control participant (with no previous melanoma) had ≥ 2 first-degree relatives with melanoma. None of the three case participants had previously been affected by melanoma, but one had two primary lesions. One control participant and one case participant, neither of whom had previously been affected by melanoma, reported having a relative with melanoma and another relative with pancreatic cancer. Three of 10 control participants who previously had been affected by melanoma had a family history of melanoma; and 1 of those 3 also had 3 primary melanomas. Six of 22 case participants who had previously been affected by melanoma had a family history of this malignancy. The overall estimated relative risk conferred by a family history of melanoma, adjusted for dysplastic nevi, age, gender, and study site, was 1.7 (95%CI, 1.1–2.7).

TABLE 2
Numbers of Case and Control Families with at Least One Affected First-Degree Relative with Specific Cancer and Associated Odds Ratios

	No. of families (%)			
Cancer type	Case	Control	OR	95% CI
Total	737 (100.0)	1021 (100.0)	—	—
Melanoma	60 (8.1)	44 (4.3)	1.71[a]	1.10–2.66
Pancreatic	13 (1.8)	16 (1.6)	1.12[b]	0.54–2.32
Gastrointestinal	101 (13.7)	125 (12.2)	1.12[b]	0.84–1.48
Brain	15 (2.0)	14 (1.4)	1.42[b]	0.69–2.94
Breast	70 (9.5)	86 (8.4)	1.13[b]	0.81–1.58
Lymphoproliferative	41 (5.6)	41 (4.0)	1.37[b]	0.88–2.14

OR: odds ratio; 95% CI: 95% confidence interval.
[a] Adjusted for age, gender, dysplastic nevi, and study site.
[b] Adjusted for family history of melanoma.

Although family histories of pancreatic, gastrointestinal, brain, breast, or lymphoproliferative malignancies each were associated with a slight increase in risk, none of these increases was significant (Table 2). The most frequent gastrointestinal malignancy in both case and control families was colorectal cancer (50 case families, including 4 that also were affected by melanoma; 71 control families, including 9 that also were affected by melanoma). Only one control participant reported having a relative with soft tissue sarcoma. Very few families contained multiple members with the same reported malignancy. Although family counts were limited, more case families than control families (3 families vs. 1 family) had both brain malignancy and melanoma in separate relatives, and this trend was similar with respect to lymphoproliferative malignancy and melanoma in separate relatives as well (6 families vs. 2 families). Because differences in families with breast, brain, and lymphoproliferative malignancies between cases and controls were not significant, these malignancies were not examined any further for familial heterogeneity. In contrast, because of consistent reports of an association with pancreatic cancer and possibly with other gastrointestinal malignancies in melanoma-prone families,[11–15] we conducted familial heterogeneity analyses of these malignancies with and without concomitant melanoma.

The disease status of family members, as expected, had a strong influence on the value of T_{ik}. All families in which at least one relative was reportedly affected by melanoma also had positive T_{ik} values.

TABLE 3
Observed Variance and Number of Families with Familial Heterogeneity (T_{ik}) > 0 According to Cancer Type among Case Families

Cancer type	Observed variance	Level of significance for observed variance	No. of families with $T_{ik} > 0$
Melanoma	4.61	0.04[a]	62
Pancreatic	0.61	0.38	13
Digestive	0.54	0.84	74
Melanoma and pancreatic	2.42	0.23	74
Melanoma and digestive	1.04	0.37	137

[a] Significant at $P < 0.05$.

TABLE 4
Number of Melanoma-Prone Families with a Proband Tested for *CDKN2A* Mutation Status by Test Statistic Level

	T_{ik}	
Measure	≤ 0	> 0
No. of families	675	62
No. of families with DNA tested	111	22
No. of mutations detected	2	1
Mutations detected	−34G→T; IVS2-4G→C[a]	G101W

T_{ik}: test statistic for the number of families with familial heterogeneity. (For further details, see Materials and Methods.)
[a] IVS2-4G→C mutation of undetermined significance.

Among case families, statistically significant familial heterogeneity was noted only with respect to melanoma (variance, 4.61; $P = 0.04$) (Table 3). There was no significant evidence of familial variation in pancreatic cancer or digestive cancer risk with or without concomitant melanoma (Table 3). To test the overall reporting of cancer in relatives, we assessed the variation in risk for all cancers combined, and this assessment yielded no evidence of familial heterogeneity ($P = 0.98$).

To determine whether any of the patients with melanoma had increased susceptibility as a result of a mutation, we screened for *CDKN2A* germline mutations in 133 melanoma case probands from whom DNA was available (Table 4). Of the tested probands, 111 were in case families that had $T_{ik} \leq 0$. One hundred one of those samples tested negative; 6 samples contained the common polymorphism A148T;[27,28] 1 sample contained the disease-related −34G→T mutation;[29,30] 1 sample contained an IVS2-4G→C mutation, the significance of which is currently unknown; and 2 samples were not amplified. Neither of the probands harboring the −34G→T or IVS2-4G→C mutation had multiple primary melanoma, and neither had other family members with melanoma. The ages of these probands were 38 years and 31 years, respectively.

The 22 remaining probands with melanoma who were tested for *CDKN2A* mutations were from families with positive T_{ik} values. One proband harbored the disease-related G101W missense mutation, and the remaining 21 had negative findings. Among those who tested negative was a proband from the only identified melanoma–pancreatic cancer family. The proband with the G101W mutation had 1 primary melanoma and her age was 35 years; her father was diagnosed with melanoma at age 58 years, but there were no other reports of cancer history in her family. The G101W mutation has been identified as a *CDKN2A* founder mutation that is believed to have originated in southwestern Europe.[31] The G101W proband reported here had genotypes consistent with the common disease-related haplotype previously reported (data not shown). There was no significant difference in mutation detection according to T_{ik} value (or equivalent family history) between families with positive T_{ik} values and families with negative T_{ik} values ($P = 0.42$).

DISCUSSION

In the current large, clinic-based study, we found an increased risk of melanoma in association with family history of melanoma, although risk increases associated with family histories of other melanoma-associated malignancies were not noted. We also found evidence of familial heterogeneity in the risk of melanoma among case families compared with the hypothetically constructed families. Families were identified as having an increased risk of melanoma via comparison with an equal-sized group of unrelated individuals who were matched with respect to age, gender, and birth cohort. However, we did not detect heterogeneity in the risk of pancreatic or other digestive cancers among relatives of cases compared with the hypothetically constructed families. Among patients with melanoma, germline mutations in *CDKN2A* were uncommon. Although only a limited number of mutations were detected, higher T_{ik} values were not significantly associated with an increased probability of finding a mutation within a given family.

The observed increase in melanoma risk in association with a family history of melanoma was consistent with the risks identified in a metaanalysis of multiple case–control studies.[32] The point estimate was slightly lower in the current study (1.7; 95% CI, 1.1–2.7) compared with the metaanalysis estimate (2.24; 95% CI, 1.76–2.86). The percentage of case participants who reported having a positive family history was

consistent with other studies, but the percentage of control participants in the current study who reported a family history of melanoma was slightly higher. Individuals who had such a family history and who had personal concerns regarding other exposures may have been more willing to participate in a study that included a full-body skin examination at a medical center that is well known for melanoma treatment. We did not detect an increased risk of developing other malignancies previously found to be associated with familial melanoma, although the relatively small number of nonmelanoma malignancies in the families made risk estimates for such malignancies unstable. These findings suggest, however that clinical screening for these other malignancies in family members of patients with melanoma in the general population is not warranted, on the basis of family history of melanoma alone.

Our findings are broadly consistent with those made in the population-based study conducted by Aitken et al.,[5] who also found significant evidence of heterogeneity in melanoma risk (as compared with the expected risk based on family size) among family members of patients with melanoma. In the current study, the reported variance was somewhat greater than the variance observed in the Aitken et al. study, and a larger proportion of families (8.3% vs. 4.7%) exhibited significant heterogeneity ($P < 0.025$), although a smaller proportion reported a positive family history of melanoma (8% vs. 19%). Thus, in the current American study sample, family and personal medical history alone would have identified families as having an elevated melanoma risk. In contrast, in Australia, where, due to increased sun exposure, melanoma is more common, familial clustering could occur more frequently by chance alone or as a result of increased clustering of environmental or host risk factors. It may be worthwhile to apply these statistical methods to such a population to identify families that are more likely to harbor genetic variations. Another factor contributing to the disparity in findings between our group and Aitken et al. is the difference in study design. Aitken and colleagues' study was a population-based effort that used a self-administered questionnaire for probands and relatives; 24% of the probands had melanoma in situ, and melanoma diagnoses in relatives were validated. In the current study, data on individual risk factors for relatives were not collected, and fewer families were included in the analysis.

In this study, T_{ik} values did not discriminate well between families with and without mutations in the major melanoma susceptibility gene, *CDKN2A*. Of the 2 families that were found to harbor known melanoma-associated mutations, one was in the $T_{ik} \leq 0$ group, whereas the other was in the $T_{ik} > 0$ group. The use of positive family history as a surrogate marker for high risk would have yielded similar results. Of the 737 case participants, 60 had 1 first-degree relative with melanoma, but only 3 had ≥ 2 first-degree relatives with melanoma. (Two were tested, and neither had a mutation in *CDKN2A*.) Other investigators also have found few mutations in families with 2 (mutation rate, $< 5\%$) or ≥ 3 (mutation rate, 20%) members affected by melanoma.[2,7] Our results suggest that case–control studies are not an efficient method for identifying individuals or families that are genetically susceptible to melanoma. Our findings also support the hypothesis that alterations in *CDKN2A* do not play a major role in the occurrence of melanoma in unselected individuals in mixed populations in contrast to multiple case families, such as those selected for linkage studies.[2,6,9,33] Even among family history–positive cases in this study, mutations were uncommon.

To evaluate the yield associated with *CDKN2A* testing of individuals with melanoma in the general population, we estimated the number of individuals who could be identified with *CDKN2A* mutations in the United States each year. In the current study, 1% of all cases had ≥ 3 family members affected by melanoma. In most settings, 20% of patients with such a family history have a positive mutation status.[7] This estimate (0.2%) is equivalent to the rate found in Aitken and colleagues' population-based study.[6] We also assumed, as an overall estimate, that 10% of individuals with multiple primary melanomas had *CDKN2A* mutations.[7] According to Surveillance, Epidemiology, and End Results Program data, 2% of all patients with melanoma develop multiple primary melanomas (unpublished data). To maximize the total number of individuals who could be identified, we assumed complete independence of family history of melanoma and the development of multiple primary lesions (which is unlikely). Thus, if all 55,100 patients diagnosed with melanoma in the United States in 2004 were tested for *CDKN2A* mutations, then only 110 individuals with a family history of melanoma and 110 individuals with multiple primary lesions would be expected to harbor germline *CDKN2A* mutations.

Previous studies have demonstrated an association between pancreatic cancer and *CDKN2A* mutation status as well as an association between pancreatic malignancy and family history of melanoma.[11–15] Thus, we sought to evaluate the relation between melanoma and pancreatic and other digestive malignancies in family members in the current study population. We did not find a significantly increased risk of melanoma in association with a family history of pancreatic or gastrointestinal malignancy. Only 1 of 737

case probands was identified as having one first-degree relative who had melanoma and another first-degree relative who had pancreatic cancer, and this proband did not have a *CDKN2A* mutation. Although we could not demonstrate an increased risk of melanoma in association with a family history of pancreatic or gastrointestinal malignancy, because of the existence of multiple consistent reports of such associations,[11–15] we assessed risk heterogeneity among case families. No evidence of heterogeneity in terms of pancreatic or digestive malignancy risk was noted in these families. In addition, no family confirmed to be harboring a *CDKN2A* mutation contained members with pancreatic cancer, and, as discussed above, *CDKN2A* mutations were not detected in the lone family affected by both melanoma and pancreatic cancer. Overall, we could not detect an association between melanoma and a family history of pancreatic or digestive malignancy in this large population of unselected patients with melanoma. Thus, screening for pancreatic cancer among family members of unselected patients with melanoma does not appear to be justified.

Information on *CDKN2A* mutation status in families affected by melanoma and breast cancer ($n = 5$), melanoma and brain cancer ($n = 3$), or melanoma and lymphoproliferative malignancy ($n = 6$) was limited. No *CDKN2A* mutations were found in probands from the melanoma-breast ($n = 3$), melanoma-brain ($n = 2$), or melanoma-lymphoproliferative ($n = 3$) families for whom DNA samples were available. Due to the limited number of families tested, there was little additional information with which to evaluate reported associations involving breast cancer and *CDKN2A* mutations[13] or associations between large germline deletions and melanoma–brain malignancy.[17,18] Breast-melanoma families in the current study were not tested for *BRCA2* mutations, although none of the families for whom samples were available had multiple breast or breast and ovarian malignancies.

Our study had several limitations. For example, we were unable to confirm cancer diagnoses in the relatives of cases or controls, and data on risk factors in the relatives of probands were not available. Previous reports from the United States, however, have indicated good agreement with reports of a family history of malignancy[34] (and melanoma in particular[35]), although other reports have indicated lower confirmation rates in the United States and in Australia.[6,36] Because we had information only on first-degree relatives, some melanoma-prone families may have gone undetected; if melanomas were reported incorrectly, then the information would have been likely to minimize differences and lead to the underestimation of heterogeneity. At the time of the current study, the relation between melanoma and pancreatic or other gastrointestinal malignancies was not widely recognized; thus, it is unlikely that there would be differential reporting among cases and controls. Study participants were well educated, with 44% of all case participants and 55% of all control participants having at least a college education. Responses to other questions indicate that the participants were relatively sophisticated with respect to medical diagnoses. Nonetheless, if there were differences in reporting between cases and controls, then the reported estimates could be biased.

In summary, we found that melanoma was the major cancer clustering in the families of patients with melanoma. Although the current investigation was a large case–control study, few families containing multiple members with melanoma were identified. The occurrence of pancreatic cancer in family members was rare, as was the occurrence of other cancers previously reported to cluster in melanoma families. The paucity of *CDKN2A* mutations found in putative high-risk families in the current study, which is consistent with other studies in this regard, suggests that other susceptibility genes may be involved in the etiology of melanoma. These findings also suggest that widespread testing for *CDKN2A* in the general population is not warranted at this time, a conclusion that is in agreement with the recommendations of the Melanoma Genetics Consortium.[37]

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